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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,817	REISBERG, BARRY	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,15-26,28,31-45,47,50-59,61 and 64-70* is/are pending in the application.

4a) Of the above claim(s) *1-7,10,15-22,31-42,45,50-55,64-66 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9,23-26,28,43,44,47,56-59,61,67,69 and 70* is/are rejected.

7)☒ Claim(s) *26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10, 15-26, 28, 31-45, 47, 50-59, 61 and 64-70 are presented for examination.

Applicant's Amendment filed October 17, 2005 has been received and entered into the application. Accordingly, the specification at pages 1, 8 and 19-20 has been amended; claims 11-14, 27, 29-30, 46, 48-49, 60 and 62-63 have been cancelled; claims 67-70 are newly added, claims 8-9, 23-26, 28, 43-44, 47, 56-59 and 61 are amended; and claims 1-7, 10, 15-22, 31-42, 45, 50-55, 64-66 and 68 remain withdrawn from consideration due to the requirement for restriction and have not been examined.

Applicant's Exhibits A through K submitted with the Amendment filed October 17, 2005 have each been considered in light of the accompanying remarks and amendments to the specification and claims.

In light of the above amendments and accompanying remarks, the objections to the specification; the rejection of claims 9, 26, 44 and 59 under 35 U.S.C. 112, second paragraph, and the rejection of claims 8-9, 43-44 and 56-59 under 35 U.S.C. 102(b), as set forth at pages 8-14 of the previous Office Action dated July 14, 2005, have each been hereby **withdrawn**.

In light of the cancellation of claims 11-14, 27, 29-30, 46, 48-49, 60 and 62-63, the rejection of claims 11-14, 46 and 48-49 under 35 U.S.C. 112, second paragraph and the rejection of claims 11, 13, 46, 48, 60 and 62 under 35 U.S.C. 102(b) have each been hereby rendered **moot**.

Finality of the Requirement for Restriction/Election

Applicant affirms the election of the following combination of agents in the remarks accompanying the amendment filed October 17, 2005:

(A) Section A (the at least one first agent): Group I, claims 1, 23, 36 and 56, wherein the at least one first agent is minocycline or any tetracycline family derivative capable of crossing the blood brain barrier;

(B) Section B (the at least one second agent): Group XVIII, claims 23, 36 and 56, wherein the at least one second agent is salicylates; and

(C) Section C (the at least one second agent, now noted as the third agent, which is an inhibitor of glutamate induced excitotoxicity): Group XXII, claims 28 and 61, wherein the at least one second agent (now noted as the third agent), is memantine.

Applicant's further election of the combination of agents noted as (4), wherein one agent of Section A is in combination with one agent of Section B, which is in combination with one agent of Section C has also been noted.

At this time, for the reasons already made of record at pages 2-8 of the previous Office Action dated July 14, 2005, the restriction requirement is deemed proper and is made **FINAL**.

Claims 1-7, 10, 15-22, 31-42, 45, 50-55, 64-66 and 68 are **withdrawn** from further consideration pursuant to 37 C.F.R. 1.142(b), as being to non-elected inventions, there being no allowable generic or linking claim. Newly added claim 68 is properly withdrawn from consideration because it does not read upon those active agents that were elected (i.e., the claim fails to read upon the use of salicylates as the second agent).

The claims corresponding to the elected subject matter are 8-9, 23-26, 28, 43-44, 47, 56-59, 61 and newly added claims 67 and 69-70, which also read on the elected subject matter, and such claims are those that have been acted on the merits.

Applicant's Request for Rejoinder

Applicant has courteously requested rejoinder of claims 15, 16, 17, 18, 31, 32, 33, 34, 50, 51, 64 and 65 at page 18 of the reply filed October 17, 2005. Applicant states that they read on the subject matter (i.e., anti-inflammatory agents) of the claims currently elected for prosecution.

However, Applicant is reminded that Applicant was required to, and did specifically elect, the species of salicylates as the anti-inflammatory agent (i.e., the at least one second agent from Section B). Examination of the claims was performed to the extent that they read upon the elected species of agent and was not performed based on the genus of "anti-inflammatory agents" as a general class.

In light of the fact that the subject matter of claims 15, 16, 17, 18, 31, 32, 33, 34, 50, 51, 64 and 65 do not read upon the elected species of salicylates as the anti-inflammatory agent, such claims are properly withdrawn from consideration during prosecution. Thus, Applicant's request for rejoinder of such claims has been carefully considered, but is, respectfully, denied.

Objection to the Claims

Claim 26 is objected to for reciting "The therapeutic method of claim 23..." in line 1 of the claim, which is inconsistent with its parent claim, independent claim 23, which is simply drawn to "A method...". Applicant may wish to consider amending the claim in the following manner, but is reminded that the acceptance of such a suggestion does not necessarily equate to the claims being free of the cited prior art.

---23. The ~~therapeutic~~ method of claim 23, wherein the at least one first agent is selected from the group consisting of...and sodium butyrate.---

Claim Rejection - 35 USC § 112, First Paragraph (New Ground of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61 and 67-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the treatment of Alzheimer's disease or other degenerative cognitive diseases, such as age-associated memory impairment, mild cognitive impairment, cerebrovascular dementia, insofar as Applicant has defined "treatment" to encompass "the identification of treatment populations at risk for a neurodegenerative condition prior to development of a neurodegenerative condition, e.g., prior to development of MCI, Alzheimer's disease or cerebrovascular dementia" (see present specification at paragraph [0022] at pages 6-7). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The present rejection is made upon reconsideration of the claims, the present disclosure and the state of the art with regard to the treatment of neurodegenerative diseases, such as Alzheimer's disease, where the unpredictability of the art would lead the skilled artisan to undue experimentation to determine how the presently claimed active agent(s) was capable of treating such conditions as elusive and difficult to diagnose as those recited in the present claims in the manner in which Applicant has defined "treatment".

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation. The Examiner has noted the variety of conditions to which Applicant has claimed invention using the claimed composition. For the purposes of consideration under 35 U.S.C. 112, first paragraph, the Examiner has focused on the specific condition of Alzheimer's disease. However, the reasons stated here concerning the burden of enabling the treatment of Alzheimer's disease apply also to the other above-mentioned conditions, but for the obvious difference in the type of disorder.

Factors 1 and 2) The present invention is drawn to a method for treating age-associated memory impairment (AAMI), mild cognitive impairment (MCI), Alzheimer's Disease (AD) or cerebrovascular dementia (CVD) and related retrogenic degenerative diseases, comprising administering a therapeutically effective amount of an agent capable of inhibiting neuronal cell cycle progression, such as minocycline or any tetracycline capable of crossing the blood brain barrier, in combination with an agent capable of inhibiting activated microglial-induced

mitogenic stimulation, such as salicylates, further in combination with an agent capable of inhibiting glutamate-induced cytotoxicity, such as memantine. Applicant defined "treatment" to include "the identification of treatment populations at risk for a neurodegenerative condition prior to development of a neurodegenerative condition, e.g., prior to development of MCI, Alzheimer's disease or cerebrovascular dementia." (see Applicant's disclosure at pages 6-7, paragraph [0022]).

Factors 3 and 7) In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that patients at risk for a neurodegenerative disease, such as, for example, Alzheimer's disease, could be effectively identified and treated with the claimed active agent(s) prior to the development of such a condition, since such a situation would essentially amount to the prevention of such a condition, since it had not yet developed in the subject. Based on the state of the art, as discussed below, the artisan would have only accepted that the symptoms and conditions outwardly exhibited by a person afflicted with Alzheimer's disease could be ameliorated, rather than that the disease itself or the progression or worsening of such a disease could actually be slowed, stopped or prevented.

As set forth in *In re Marzocchi et al.,* 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming

that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added).

The term "treat" in the present claims is a term that, interpreted in its broadest sense in accordance with the MPEP at §2111, circumscribes various scenarios, including the amelioration of symptoms, the disappearance of symptoms, slowing or halting the progression of such a disease or identifying patients at risk for a neurodegenerative condition prior to developing such a neurodegenerative condition and treating them with the presently claimed combination of active agents. Identifying patients at risk prior to developing the disorder would essentially amount to the prevention of such a disorder in those patients. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed combination of active agents, the development, progression or worsening of Alzheimer's disease would be prevented, slowed or arrested, that the symptoms associated with such a condition would disappear or be significantly lessened and that there would be a reasonable guarantee that Alzheimer's disease would not progress to the point of being incapable of basic human function. Such a situation is sufficiently unusual that data would need to be shown in order to establish that Alzheimer's disease could be kept from ever developing, progressing or worsening or that the symptoms directly associated with such a condition would be eradicated or significantly lessened through the administration of the claimed active agent. Because absolute success is not reasonably possible with most diseases or disorders, especially a condition as complex and poorly understood as Alzheimer's disease, the specification, which lacks an objective showing that such a disease could be treated in such a manner, is viewed as

lacking an enabling disclosure of the same.

Here, the objective truth of the statement that Alzheimer's disease may be treated as defined by Applicant is doubted. Alzheimer's disease is particularly elusive and manifests itself in a variety of different ways in different subjects such that one cannot be entirely sure that the disease is truly the cause of the signs and symptoms of disorder exhibited by the patient. A diagnosis of Alzheimer's disease is tentative, at best, until confirmation of the diagnosis can be confirmed by the presence of amyloid deposits in the brain at autopsy (see Cecil's Textbook of Medicine, "Differential Diagnosis", page 2043 at column 1).

Such difficulties in diagnosis are recognized in the art. Applicant's attention is drawn to Cecil's Textbook of Medicine, which states, "In a patient with clinical findings suggesting Alzheimer's disease, other causes of dementia should be excluded by history, examination, and the laboratory studies described above. CSF evaluation for amyloid protein and tau protein can increase the likelihood of a diagnosis of Alzheimer's disease, but they are not sufficiently specific to be of routine value in screening or early diagnosis of Alzheimer's disease...Presence of the apoE4 allele makes it very likely that the patient's dementia is produced by Alzheimer's disease. ApoE testing does not have predictive value for asymptomatic individuals." (see Cecil's Textbook of Medicine, "Diagnosis", column 2 at page 2044)

In this regard, it is also noted that the art acknowledges only certain criteria for definitive diagnosis of Alzheimer's disease, see in particular Gauthier et al., (Can. Med. Assoc. J, Oct 15, 1997, 157(8): 1047-52), Greicius et al. (J Neurol. Neurosurg. Psychiatry, 2002 Jun; 72(6):691-700) and Gasparini et al. (FASEB J., 12, Jan. 1998, pp. 17-34). Post mortem analysis of brain tissue for the characteristics of amyloid plaques is considered necessary. This is because the art

has come to recognize its presence in essentially all cases. However, to achieve diagnostic status took years of evaluative procedures, both pre- and post-mortem, confirming that every case had a degree of this pathology. Even so, diagnostic application is often problematic given variable peptide expression patterns among clinically similar and dissimilar diseases states (see Greicius et al.).

Given that there a only a few factors that are recognized to have moderate, if any, predictive value in determining the likelihood that patients develop such a disease or to determine whether patients actually have such a disease, since many of the early signs of Alzheimer's disease are common complaints of aging or resulting from other neurological conditions, such as depression, where memory impairment is not present (see Cecil's Textbook of Medicine, "Evaluation of Dementia", column 1, page 2042), one of ordinary skill in the art would not accept on its face Applicant's statement that Alzheimer's disease could simply be treated, in the manner that Applicant has defined, using the presently claimed active agents. Not only is the population in need of such treatment not well defined in the art because of the difficulties associated with making an accurate diagnosis, but the disease is also sufficiently complicated and poorly understood such that the idea that any active agent (including that presently claimed) would be capable of preventing, slowing or halting the progression or worsening of the symptoms, or that such symptoms would disappear or be significantly lessened upon administration of such an agent, would not have been reasonably expected by the skilled artisan. The artisan would have required sufficient direction as to how the administration of the presently claimed active agent(s) could actually determine the population of patients in need of such treatment and how the presently claimed agent(s) could treat the development of

Alzheimer's disease such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected given that the concept of a single agent, or even a combination of agents, that is effective against the development of Alzheimer's disease or that is effective in eradicating or lessening the symptoms associated with Alzheimer's disease would have been unique and, thus, met with a great deal of skepticism.

Factor 4) Applicant has merely disclosed that by administering any of the claimed active agents in a patient with Alzheimer's disease, or any one of the other above-mentioned disorders, one may treat such a condition in a patient. Based on the discussion in Section 3 above, however, such disclosure clearly is not adequate direction or guidance as to how the proposed combination of active agents could be employed to accomplish the treatment of Alzheimer's disease, or any of the other conditions, in a predictable manner.

Factor 5) The specification merely discloses that use of the presently claimed active composition has activity in the treatment of Alzheimer's disease. Although Applicant discloses that "treatment", in the manner defined by Applicant, may be achieved, the instant specification does not provide guidance as to how one skilled in the art would accomplish such an objective of treating Alzheimer's disease or any of the above-mentioned neurodegenerative conditions since it cannot be reasonably guaranteed that the progression of such a condition may be prevented, slowed or arrested. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active agent for the treatment of such a condition.

The Examiner acknowledges that the Office does not require the presence of working

examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the unpredictable nature of identifying patients afflicted with Alzheimer's disease, the Office would require appropriate data to support the contention that the use of the claim specified active agent(s) could actually treat Alzheimer's disease in the manner defined by Applicant by simply administering, by any method, an amount of the claimed combination of active agents, since the present specification fails to enable one of ordinary skill in the art to practice such an aspect of the presently claimed invention.

Factor 6) The burden of enabling the treatment or prevention of Alzheimer's disease is much greater than that of enabling the improvement of the individual symptoms resulting from such a condition. Since the present specification would not enable the skilled artisan to treat Alzheimer's disease, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice this aspect of the invention.

Factor 8) In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the treatment of Alzheimer's disease, or any one of the above-mentioned conditions, in the manner defined by Applicant, could be achieved. In order to actually achieve treatment of this condition, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. §112, first paragraph.

Given that the art fails to recognize and Applicant has failed to demonstrate that Alzheimer's disease, or any of the above-mentioned disorders, could effectively or absolutely be treated, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61 and 67-70 are deemed properly rejected.

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-9, 43-44, 47 and 67-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention, for the reasons already made of record at pages 10-11 of the previous Office Action dated July 14, 2005.

Cancellation of claims 11-14, 46 and 48-49 renders the present rejection of such claims under 35 U.S.C. 112, second paragraph, **moot**.

Newly added claims 67-68 are properly included in the present rejection because each is drawn to a method for treating related retrogenic degenerative diseases.

Applicant's amendments and remarks have each been carefully considered in their entirety, but fail to be persuasive in establishing error in the propriety of the present rejection.

Applicant states that one of skill in the art is capable of ascertaining what cognitive and neurologic diseases fall within the meaning of this term and which diseases would be considered a "related retrogenic disease" as defined in the present specification. Applicant relies upon the

present specification at paragraph [0033] and Applicant's submitted document labeled "Exhibit A" in support of their position that the term "related retrogenic diseases" is not indefinite.

The term "retrogenesis" is not what is in dispute in the present rejection. Rather, it is the fact that Applicant has claimed the treatment of "related retrogenic diseases" (see present claim 8, for example), but still has not adequately defined and delimited those diseases that Applicant intends to be within the scope of such a term, how the diseases are "related" to retrogenesis and the degree of similarity a condition must have to retrogenesis *per se* and still be considered a "related" retrogenic disease.

Applicant reliance upon paragraph [0033] of the present specification to define the term "retrogenesis" and to further state that the retrogenic process "is also related to recent findings regarding the molecular biology of normal cellular development and the changes in these normal molecular processes in AD, CVD and other retrogenic dementias" and that activation of "mitogenic molecular markers including the mitogen-activated protein kinase (MAPK) cascade, cyclins, and cyclin dependent kinases" has been "related to the phosphorylation and hyperphosphorylation of tau, and, consequently, the development of neurofibrillary changes in AD" has been carefully considered, but still fails to adequately define or delimit those diseases that are intended to be within the scope of the present claims.

For example, the word "related" is a term that is open to subjective interpretation as to whether a particular disease state is considered to be a condition associated with retrogenesis. In light of such a subjective interpretation, and further in light of the fact that the presently claimed subject matter and corresponding disclosure does not particularly point out the degree or type of relationship that a given retrogenic condition may have to those that are presently claimed and

still be considered a retrogenic disease as intended by the claims, the metes and bounds of the term and, thus, the claim, cannot be identified.

It is again noted that Applicant has not set forth in a reasonably clear, deliberate or precise manner what other diseases would be considered "related" retrogenic diseases in either the claims, disclosure or response to the previous Office Action such that one skilled in the art would be able to determine whether a given condition was properly characterized as a related retrogenic disease through the measurement of cognitive and/or overall function. Absent such direction, the phrase "related retrogenic disease" is open to subjective interpretation and does not properly limit the claim. Should Applicant intend the treatment of specific conditions that Applicant has determined to be related to retrogenesis, it is suggested that Applicant may wish to consider amending the claims to add such limitations. However, it remains that the phrase "related retrogenic disease" fails to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, absent any disclosure or persuasive remarks to the contrary, and the claims are, therefore, properly rejected.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61, 67 and 69-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan (WO 02/020022; March, 2002) in view of Lipton (WO 92/17168; 1992), Lee et al. (U.S. Patent No. 6,043,224; 2000) and Gervais et al. (U.S. Patent Application Publication No. 2005/0031651; Published 2005, Priority to U.S. Provisional Application No. 60/482,214 filed June 2003), each already of record, for the reasons already made of record at pages 14-17 of the previous Office Action dated July 14, 2005, and further in view of newly cited Morris et al. ("Mild Cognitive Impairment Represents Early-Stage Alzheimer's Disease", 2001), cited in response to Applicant's remarks.

Cancellation of claims 11-14, 27, 29-30, 46, 48-49, 60 and 62-63 renders the present rejection of such claims under 35 U.S.C. 103(a) **moot**.

Newly added claims 67 and 69-70 are properly included in the present rejection because the combination of minocycline (or a tetracycline compound), salicylates and memantine for the treatment of Alzheimer's disease or other cognitive disorders would have been obvious to one of ordinary skill in the art because each was separately known to have efficacy in the treatment of Alzheimer's disease and would have been reasonably expected to have, at minimum, additive, if not synergistic, effects when combined. Furthermore, the reasonable expectation of additive, if not synergistic, effects when combined for treating Alzheimer's disease would have also increased the reasonable expectation of success in treating other disorders associated with cognitive decline, since the other presently claimed cognitive disorders were known to have similar pathophysiological manifestations as Alzheimer's disease (i.e., related to amyloid peptide) and would have been reasonably expected to react similarly to such a therapeutic combination of agents as Alzheimer's disease itself.

Response to Applicant's Arguments

Applicant's amendments and remarks have each been carefully considered in their entirety, but fail to be persuasive in establishing error in the propriety of the present rejection.

Applicant's remarks will be addressed in the order in which they were presented in the Amendment filed October 17, 2005.

(1) The Duncan, Lee et al., Lipton or Gervais et al. References

Applicant asserts that Duncan, Lee et al., Lipton or Gervais et al. does not teach or suggest the use of a composition comprising at least one first agent that is an inhibitor of neuronal cell cycle progression, such as tetracycline, combined with at least one second agents, such as an anti-inflammatory, combined with a third agent, such as an inhibitor of glutamate induced excitotoxicity, all as described in the present application, for the treatment of AAMI, MCI or cerebrovascular dementia.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Examiner did not assert in the previous Office Action dated July 14, 2005 that any one or more of the cited references taught the presently claimed invention in its entirety. However, the citation of Duncan, Lee et al., Lipton and Gervais et al., *in combination* (emphasis added), render the presently claimed

subject matter obvious for the reasons already made of record at pages 14-17 of the previous Office Action.

In further response to Applicant's assertion that the use of memantine for treating moderate to severe Alzheimer's disease was not approved by the FDA until September 2003 following a study conducted by the present inventor (the results of which were not published until after the priority date of the present application) has been carefully considered, but fails to be persuasive. FDA approval or disapproval of a drug or a drug combination is a separate and distinct issue from the determination of patentability and has no bearing on such a determination. In other words, patentability does not hinge on whether the FDA has approved or disapproved a drug or a drug combination for the treatment of a particular disease state.

Moreover, Applicant's attention is directly expressly to the Lipton reference at pages 4, lines 23-31, page 10, lines 14-17 and page 10, line 32-page 11, line 3, which clearly teaches and suggests the use of the NMDA receptor blocking compound memantine for the treatment of Alzheimer's disease. Thus, regardless of whether the FDA had approved such a drug for the treatment of such a disease, such does not change the fact that Lipton expressly teaches such a drug for the treatment of such a disease and, thus, is sufficient motivation for one of ordinary skill in the art to have contemplated the use of such a compound for the treatment of Alzheimer's disease.

(2) The Analysis under 35 U.S.C. 103(a)

Applicant submits that the combination of Duncan, Lee et al., Lipton and Gervais et al. do not teach or suggest the presently claimed subject matter, nor would one be motivated to

combine the teachings of Duncan with those of Lee et al., Lipton and Gervais et al. because there would not have been a reasonable expectation of success if one were to make such a combination. Applicant states that the present application differs markedly from Duncan in that it suggests the utility of minocycline and related tetracycline compounds because of cell cycle inhibitory effects, not anti-inflammatory effects, and, therefore, the dosage, endpoint and goal of administration are different from those proposed by Duncan.

In response to Applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this instant case, it has been clearly stated on the record that one of ordinary skill in the art would have been motivated to combine the active agents taught by Duncan, Lee et al. and Lipton because Duncan teaches minocycline (or a tetracycline compound), Lee et al. teaches aspirin or salicylic acid or other salicylates, and Lipton teaches memantine, each for the therapeutic objective of treating Alzheimer's disease and other neurodegenerative diseases. Motivation to administer the three compounds together flows logically from the efficacy of each compound in treating Alzheimer's disease and other neurodegenerative diseases as demonstrated in the prior art and also because each compound has been previously administered for the same therapeutic endpoints. In light of such, there is a reasonable expectation that the combination of

the three agents would successfully produce, at minimum, additive, if not synergistic, effects when combined.

Insofar as Applicant has failed to provide any further evidence in support of their position that there is no motivation to combine the cited references and that there is no reasonable expectation of success aside from Applicant's own assertions, the remarks are not persuasive and the rejection remain proper for the reasons already made of record above and in the previous Office Action.

While Applicant's remarks regarding the fact that the present application differs from Duncan in that the minocycline or tetracycline compound is used for its cell cycle inhibitory effects and not its anti-inflammatory effects, the mere fact that Applicant may have discovered another advantageous property of minocycline or a tetracycline compound in how it achieves treatment of Alzheimer's disease cannot be the basis for patentability. As already discussed above and in the previous Office Action at pages 14-17, the combination of the three agents would have been *prima facie* obvious to one of ordinary skill in the art, absent factual evidence to the contrary. It remains that Duncan teaches minocycline or a tetracycline compound for the treatment of Alzheimer's disease. Whatever property attributed to such a compound is merely a statement of its function and does not change the fact that it was well known in the art at the time of the invention for the treatment of Alzheimer's disease and other neurodegenerative conditions and its use for such an objective would have been obvious to the skilled artisan.

Furthermore, Applicant has merely claimed a "therapeutically effective amount". Absent factual evidence to the contrary, the amounts taught by Duncan are also considered to be "therapeutically effective amounts" in that the amount administered is effective for achieving the

therapeutic treatment of the intended disease or disorder (i.e., Alzheimer's disease or other neurodegenerative conditions). Thus, the amounts do not appear to differ, despite Applicant's assertions to the contrary.

(3) Regarding the Use of Anti-Inflammatory Agents (e.g., salicylates) for Treating Alzheimer's Disease

Applicant asserts that, in fact, the anti-inflammatory approach to the treatment of Alzheimer's disease has not been successful as a first approach and relies upon the teachings of Aisen et al. (see Exhibit B), who showed that rofecoxib and naproxen did not slow cognitive decline in patients with mild to moderate Alzheimer's disease, and Thal et al., who demonstrated that rofecoxib would not delay a diagnosis of AD. Applicant further states that no anti-inflammatory compounds have been approved by the FDA or other regulatory agencies for the treatment of AD, MCI, AAMI, cerebrovascular dementias or other retrogenic dementias and also submits that the present application does not claim an anti-inflammatory agent as the first agent in the treatment of Alzheimer's disease.

Reliance on the results shown by Aisen et al. or Thal et al. is not found to be persuasive because both Aisen et al. and Thal et al. are drawn to the use of the NSAIDs rofecoxib or naproxen, not salicylates, which is what is presently elected and is the basis for the rejection. Therefore, the lack of efficacy demonstrated by rofecoxib or naproxen in the treatment of Alzheimer's disease is not at all pertinent to the efficacy of salicylates in treating the same. Furthermore, Applicant's attention is once again directed to Lee et al., who expressly teaches the

efficacy of salicylates in the treatment of Alzheimer's disease or other neurodegenerative diseases (see Lee et al., col.5, lines 10-16; col.10, lines 38-42; and col.18, lines 25-58).

Moreover, Applicant's statement that no anti-inflammatory compounds have been approved by the FDA or other regulatory agencies for the treatment of AD, MCI, AAMI, cerebrovascular dementias or other retrogenic dementias is also not found to be persuasive. As already stated above, FDA approval or disapproval of a drug or a drug combination is a separate and distinct issue from the determination of patentability and has no bearing on such a determination.

Lastly, it is irrelevant that Applicant has not claimed an anti-inflammatory agent as the "first agent" in the treatment of the presently claimed diseases. The broadest, most reasonable interpretation of the claims simply requires that the anti-inflammatory agent (i.e., salicylates) be administered via the presently claimed method. The "importance" of the agent or the order in which it is administered has no bearing on the determination of whether it would have been obvious to the skilled artisan to employ such an agent for the treatment of the presently claimed conditions.

(4) Regarding AAMI and MCI to be Progressive Conditions Leading to Alzheimer's Disease

Applicant states that mild cognitive impairment is a condition that does not necessarily progress to frank dementia, nor does it necessarily progress to Alzheimer's disease. Applicant relies upon Exhibit D (2004), Exhibit E (2005) and Exhibit F (2005) in support of their position.

Applicant's remarks and submitted Exhibits D, E and F have been carefully considered, but are not found persuasive. Reliance upon Exhibits D, E and F cannot be afforded the

significance that Applicant has requested because they fail to show that, *at the time of the invention*, it was known in the art that mild cognitive impairment was a condition that did not necessarily progress to Alzheimer's disease.

Moreover, in further support of the position taken in the present rejection, the abstract of Morris et al. ("Mild Cognitive Impairment Represents Early-Stage Alzheimer's Disease", 2001) is cited. Morris et al. studied the condition of mild cognitive impairment and the course of progression of the disease and concluded that mild cognitive impairment generally represented early-stage Alzheimer's disease (see Conclusions).

In light of such, the relationship between mild cognitive impairment was recognized in the art *at the time of the invention* to be a disorder preceding the development of advanced Alzheimer's disease. For this reason, and those already made of record, the present rejection remains proper.

(5) Regarding the Assumption that Medications Useful in Alzheimer's Disease are Effective in Treating Other Retrogenic Diseases or Conditions

Applicant asserts that there is universal agreement that medications that are effective for Alzheimer's disease are not necessarily effective for MCI or AAMI. Applicant states that none of the medications approved for the treatment of Alzheimer's disease have been approved for the treatment of mild cognitive impairment. Applicant further states that despite studies in the mild cognitive impairment area, no medications have been approved at this time for the treatment of either mild cognitive impairment of age-associated memory impairment. Applicant relies upon the approval of donepizil, rivastigmine and galantamine for the treatment of mild to moderate

Alzheimer's disease in support of their position that this limited approval speaks volumes for the FDA's belief that a medication approved for a specific severity range does not necessarily mean that the medication is effective for other severity ranges and certainly not for other diagnoses. Applicant further relies upon Exhibit H (2005) and Exhibit I (2004) in support of their position.

Insofar as Applicant has failed to provide any further evidence in support of their position that there is universal agreement that medications effective for Alzheimer's disease are not necessarily effective for MCI or AAMI aside from Applicant's own assertions, the remarks are not persuasive.

Applicant's statements regarding approval of medications are also not found to be persuasive. As already stated above, FDA approval or disapproval of a drug or a drug combination is a separate and distinct issue from the determination of patentability and has no bearing on such a determination.

Furthermore, Applicant's statements with regard to the "FDA's belief" amount to no more than speculation on the part of Applicant as to the FDA's rationale and such statements are not persuasive. Applicant's attention is also directed to the preceding paragraph regarding FDA approval or disapproval of drugs or drug combinations and its relationship to patentability.

While submitted Exhibit H has been carefully considered, it is not found to be persuasive because it does not establish what was known in the art *at the time of the invention* and is directed towards FDA approval, which, as it has already been stated on the record, is not a relevant consideration to the determination of patentability.

Lastly, Exhibit I has also been carefully considered, but is not found to be persuasive because it is directed to cholinesterase inhibitors for the treatment of mild cognitive impairment and is not directed to those agents presently elected and examined.

(6) Regarding the Obviousness to Combine Two Agents

Applicant states that the Examiner implied that if one medication is approved for an indication and another medication is also approved for that same indication, then naturally it is obvious to everyone that both medications are better than one medication alone for that indication. Applicant submits that this reasoning does not apply to Alzheimer's disease specifically, nor should it preclude patentability of the present invention. Applicant relies upon Tariot et al. and DeSarno et al. in support of their position. Applicant also states that the present application proposes combinations of treatments that would have synergistic efficacy based on Applicant's model of retrogenesis and cell cycle inhibition.

First, Applicant's attention is drawn to the previous Office Action dated July 14, 2005 at pages 15-16. The Examiner did not expressly state that, "naturally it is obvious to everyone that both medications are better than one medication alone for that indication". Rather, the Examiner stated that the *motivation* to administer one or more drugs known in the art for the same therapeutic objective flows logically from the efficacy of each compound in treating Alzheimer's disease and other neurodegenerative diseases as demonstrated in the prior art, which *raises the reasonable expectation of success* that such a combination would have greater efficacy than one single agent alone.

Second, Applicant's statement that "this reasoning does not apply to Alzheimer's disease specifically, nor should it preclude patentability of the present invention" is not a point well taken. Applicant relies upon Tariot et al. and DeSarno et al. in support of their position. However, Tariot et al. is drawn to a combination of donepizil and memantine, which is not the combination presently elected and examined. Therefore, such results are not relevant to showing that the presently claimed combination of agents would not have been obvious to the skilled artisan.

Furthermore, Applicant's reliance on DeSarno et al. has been considered but is also not found to be persuasive because DeSarno et al. is currently in press and would not have been knowledge generally available to the skilled artisan *at the time of the invention.* Even if DeSarno et al. *had been* available to the skilled artisan at the time of the invention, it still would not have been found persuasive because it fails to address the presently claimed combination of agents.

Lastly, if Applicant intends to rely upon synergistic efficacy, Applicant must discuss and show data specifically directed to the greater than additive efficacy shown by the combination of agents over that of any single one of the agents alone. In the absence of such discussion and data, the mere assertion of synergistic efficacy is, respectfully, insufficient and is not persuasive.

(7) Regarding Amyloid and Alzheimer's Disease

Applicant states that the Examiner's attention is drawn to the fact that no treatments for Alzheimer's disease based on lowering, raising or otherwise changing beta amyloid, or any other element of amyloid plaques, have been approved in the U.S. or anywhere else at the present time.

Applicant is once again reminded that FDA approval or lack of approval of a drug or a drug combination is a separate and distinct issue from the determination of patentability and has no bearing on such a determination. In other words, approval of a drug or a drug combination is not relevant to patentability. Thus, Applicant's arguments insofar as they rely upon the fact that no treatments for Alzheimer's disease based on lowering, raising or otherwise changing beta amyloid or any other element of amyloid plaques have been approved in the U.S. or anywhere else at the present time is not found to be persuasive.

Furthermore, Applicant is reminded that it the state of the art *at the present time* is not relevant to the determination of patentability at the *time of the invention*. The prior art and analysis of adequate motivation is determined based upon the knowledge that was generally available to one of skill in the art *at the time the invention was made*, not what is presently available to one of skill in the art.

Moreover, the Examiner did not assert that the present combination of agents for the treatment of Alzheimer's disease would have been obvious because they would lower, raise or otherwise change beta amyloid. Rather, the present rejection was based upon the fact that Alzheimer's disease, and the other presently claimed cognitive impairment disorders, were known in the art to be pathophysiologically related to amyloid peptide and, therefore, therapeutic methods known in the art for the treatment of one of such disorders would have raised the reasonable expectation of success that such a therapeutic method would also have had efficacy in treating other disorders known to have similar etiology and pathophysiological manifestations. Applicant's attention is drawn to the previous Office Action at pages 16-17.

(8) Regarding Amyloid and MCI

Applicant states that the Examiner's attention is drawn to the fact that no treatments for mild cognitive impairment or age-associated memory impairment based on lowering, raising or otherwise changing beta amyloid, or any other element of amyloid plaques, have been approved in the U.S. or anywhere else at the present time.

Applicant's attention is drawn above to the rationale provided under section (7), entitled "Regarding Amyloid and Alzheimer's Disease". The same reasoning applies to Applicant's present remarks.

(9) The Relationship Between Vascular Dementia Treatment and Treatment of Alzheimer's Disease

Applicant states that if a treatment is useful for Alzheimer's disease, then it should be useful for vascular dementia is not necessarily true and relies upon a prevention study of non-steroidal anti-inflammatory drugs in support of their position, which stated that, "the long term use of NSAIDS may protect against Alzheimer's disease, but not against vascular dementia".

Reliance on such a study is not found to be persuasive. First, the study that Applicant has relied upon to discount the Examiner's conclusion that a treatment useful for Alzheimer's disease would have also been useful for vascular dementia is a prevention study. The presently claimed subject matter is drawn to a method of treating Alzheimer's disease or vascular dementia, not a method of prevention. Thus, while NSAIDs as a general class may not have shown significant efficacy in protecting against vascular dementia, such does not necessarily equate to NSAIDS not having any efficacy at all in the treatment of vascular dementia. It is

noted that any efficacy, or lack thereof, demonstrated by an agent in *preventing* a condition does not necessarily equate to the same efficacy, or lack thereof, in *treating* the same. Applicant has already admitted on the record that such is the case (i.e., it is not true that a medication used to treat an illness is likely to be useful in preventing the same condition; see first paragraph of Applicant's remarks at page 36).

Furthermore, it is noted that the claims have been examined insofar as they read upon salicylates as the anti-inflammatory agent, not simply the use of any NSAID known in the art. Thus, results obtained regarding the general category of NSAIDs are not necessarily suggestive of the same or substantially similar results regarding the species of salicylates, in particular. Moreover, it is noted that the study described by Veld et al. expressly stated that they "conducted a prospective, population-based cohort study to determine whether the use of NSAIDs ***other than aspirin*** was associated with a decreased risk of Alzheimer's disease or vascular dementia." (emphasis added; see Veld et al., last sentence of second paragraph of column 2 at page 1515) Such is further proof that the results obtained by Veld et al. are not pertinent to the present rejection because Veld et al. studied the use of NSAIDs other than salicylates in the development of vascular dementia, while the present claims were expressly drawn to the use of salicylates as the elected species of anti-inflammatory agent. In light of such, it is clear that the results obtained by Veld et al. cannot be afforded the significance that Applicant has requested.

Therefore, the determination that the use of salicylates for the treatment of vascular dementia would have been obvious remains proper, absent any factual evidence to the contrary.

(10) The Relationship Between a Medication which Prevents an Illness and a Medication which Treats the Illness

Applicant states that the Examiner implied that a medication that treats an illness such as Alzheimer's disease is likely to be useful in preventing the condition.

The Examiner cannot locate an express statement or any implied suggestion in the previous Office Action asserting that a medication useful for the treatment of an illness such as Alzheimer's disease is likely to be useful in preventing the condition.

Conclusion

Rejection of claims 8-9, 23-26, 28, 43-44, 47, 56-59, 61, 67 and 69-70 remains proper and is **maintained**.

Claims 1-7, 10, 15-22, 31-42, 45, 50-55, 64-66 and 68 are **withdrawn** from consideration.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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